

## Supplementary Material

### S1 Notes on the numerical solution of Equation 11

Consider Equation 11 in the form,

$$\text{Obj}(x) = \eta \ln x + (1 + \alpha) \ln(1 + x) - \ln C = 0.$$

Observe first that, since we require  $\eta > 0$ , the first term of our objective is strictly increasing, like the second. This guarantees a unique, positive root  $x_0$  that will readily be found by search over a suitable interval. Bounds for this search may be obtained by considering the value of  $x$  that zeroes the non- $\eta$  part of our objective:

$$\begin{aligned} X = C^{1/(1+\alpha)} - 1 &\implies (1 + \alpha) \ln(1 + X) - \ln C = 0 \\ &\implies \text{Obj}(X) \equiv \eta \ln X. \end{aligned}$$

Thus,  $X$  gives either an upper or lower bound on our root, according to the sign of  $\eta \ln X$ :

$$\begin{aligned} X \geq 1 &\implies \text{Obj}(X) \geq 0 \implies x_0 \in (0, X] \\ X < 1 &\implies \text{Obj}(X^+) < 0 \implies x_0 \in (X^+, 1), \end{aligned}$$

where  $X^+ = \max(0, X)$  denotes the positive part of  $X$ . Note that the upper bound of 1 holds in the latter case because

$$\begin{aligned} X < 1 &\implies \text{Obj}(1) = 0 + (1 + \alpha) \ln(1 + 1) - \ln C \\ &> 0 + (1 + \alpha) \ln(1 + X) - \ln C \equiv 0. \end{aligned}$$

## S2 Cost of the 1-size-fits-all dosing constraint

Here we examine, on the same axes as Figure 3, the utility lost to the 1-size-fits-all dosing constraint, according to Equation 12. Unlike  $n_{\min}$  plotted in Figure 3, however, the expected utilities in Equation 12 depend on  $(a, b)$  in a manner that cannot be subsumed into  $\tau(1)$ . So in order to exhibit contours of utility loss on the same axes as Figure 3, thereby providing some additional context for that central result of this paper, we must fix arbitrarily one degree of freedom in  $(a, b)$ , so that a mapping  $(\tau, P_{\max}, \alpha, \beta, \eta) \mapsto (a, b)$  arises. We accomplish this here by fixing IIV (IQR:median) for  $D^*$  to be 1, thereby determining  $a$ , and then solving Equation 8 for  $b(a, \tau, P_{\max}, \alpha, \beta, \eta)$ .

```
function ab(IIV,tau,P_max,alpha,beta,eta) # Given IQR(D*)/median(D*), map (tau,P_max,alpha,beta,eta) --> (a,b)
  a = a_IQR(IIV) # TODO: Does such reuse warrant renaming this function?
  # Solve Eq (8) for b in terms of (tau,D=1,P_max,alpha,beta,a,eta):
  b = ( tau * gamma(a+1+eta)/gamma(a) / EP_r(1.0; P_max=P_max, alpha=alpha, beta=beta) )^(1/(1+eta))
  @assert tau ≈ tau(1.0; P_max=P_max, alpha=alpha, beta=beta, eta=eta, a=a, b=b)
  return a, b
end

if (draft) # Thin grid to speed computation, if quarto invoked with -P draft:true.
  HED50 = range(first(HED50), last(HED50), length(HED50) ÷ 3)
  taus = exp.(range(log(first(taus)), log(last(taus)), length(taus) ÷ 3))
end

# We take care to perform the costly EUopti calculation just once, saving this
# intermediate result for plotting both absolute and relative utility losses.
EUopti = Array{Float64, 4}(undef, 3, 3, length(taus), length(HED50)) # individualized
EUopt1 = Array{Float64, 4}(undef, 3, 3, length(taus), length(HED50)) # 1-size-fits-all

function maxutil(; HED50, tau, P_max, eta) # 1st term of Eq. (9)
  alpha, beta = a_beta(IQR = HED50)
  a, b = ab(IIV=1.0, tau=tau, P_max=P_max, alpha=alpha, beta=beta, eta=eta)
  EUopt(P_max=P_max, alpha=alpha, beta=beta, eta=eta, a=a, b=b)
end
```

```

function maxu1(; HED50,  $\tau$ ,  $P_{\max}$ ,  $\eta$ ) # 2nd term of Eq. (9)
     $\alpha$ ,  $\beta$  =  $\alpha\beta$ (IQR = HED50)
    a, b =  $\alpha\beta$ (IIV=1.0,  $\tau=\tau$ ,  $P_{\max}=P_{\max}$ ,  $\alpha=\alpha$ ,  $\beta=\beta$ ,  $\eta=\eta$ )
    EU(Dtilde( $P_{\max}=P_{\max}$ ,  $\alpha=\alpha$ ,  $\beta=\beta$ ,  $\eta=\eta$ , a=a, b=b),
         $P_{\max}=P_{\max}$ ,  $\alpha=\alpha$ ,  $\beta=\beta$ ,  $\eta=\eta$ , a=a, b=b)
end

using Folds # to parallelize hcubature() over multiple cores

for p in 1:3, h in 1:3
     $P_{\max}$  = [0.8, 0.9, 1.0][p];  $\eta$  = [0.1, 0.5, 1.0][h]
    EUopti[p,h,:]= Folds.collect(maxutil(HED50=y,  $\tau=x$ ,  $P_{\max}=P_{\max}$ ,  $\eta=\eta$ )
        for x in taus, y in HED50)
    EUopt1[p,h,:]= [maxu1(HED50=y,  $\tau=x$ ,  $P_{\max}=P_{\max}$ ,  $\eta=\eta$ )
        for x in taus, y in HED50]
end

c2(p, h) = let  $P_{\max}$  = [0.8, 0.9, 1.0][p],  $\eta$  = [0.1, 0.5, 1.0][h]
    contours(taus, HED50, EUopti[p,h,:], EUopt1[p,h,:], (0.01:0.01:0.2))
end

figS1() = plot([contauiv(c2(p, h),  $P_{\max}$ =[0.8, 0.9, 1.0][p],  $\eta$ =[0.1, 0.5, 1.0][h])
    for h in 1:3, p in 1:3]..., layout=(3,3),
    xlims=(1.4,10.5), # given contours don't span x range for  $\eta=1.0$  plots
    xscale=:log10, xticks=((2:10),["2","3","4","5","","","7","","","10"])))

c3(p, h) = let  $P_{\max}$  = [0.8, 0.9, 1.0][p],  $\eta$  = [0.1, 0.5, 1.0][h]
    contours(taus, HED50, EUopt1[p,h,:], EUopt1[p,h,:], (0.05:0.05:0.95))
end

figS2() = plot([contauiv(c3(p, h),  $P_{\max}$ =[0.8, 0.9, 1.0][p],  $\eta$ =[0.1, 0.5, 1.0][h])
    for h in 1:3, p in 1:3]..., layout=(3,3),
    xscale=:log10, xticks=((2:10),["2","3","4","5","","","7","","","10"])))

```

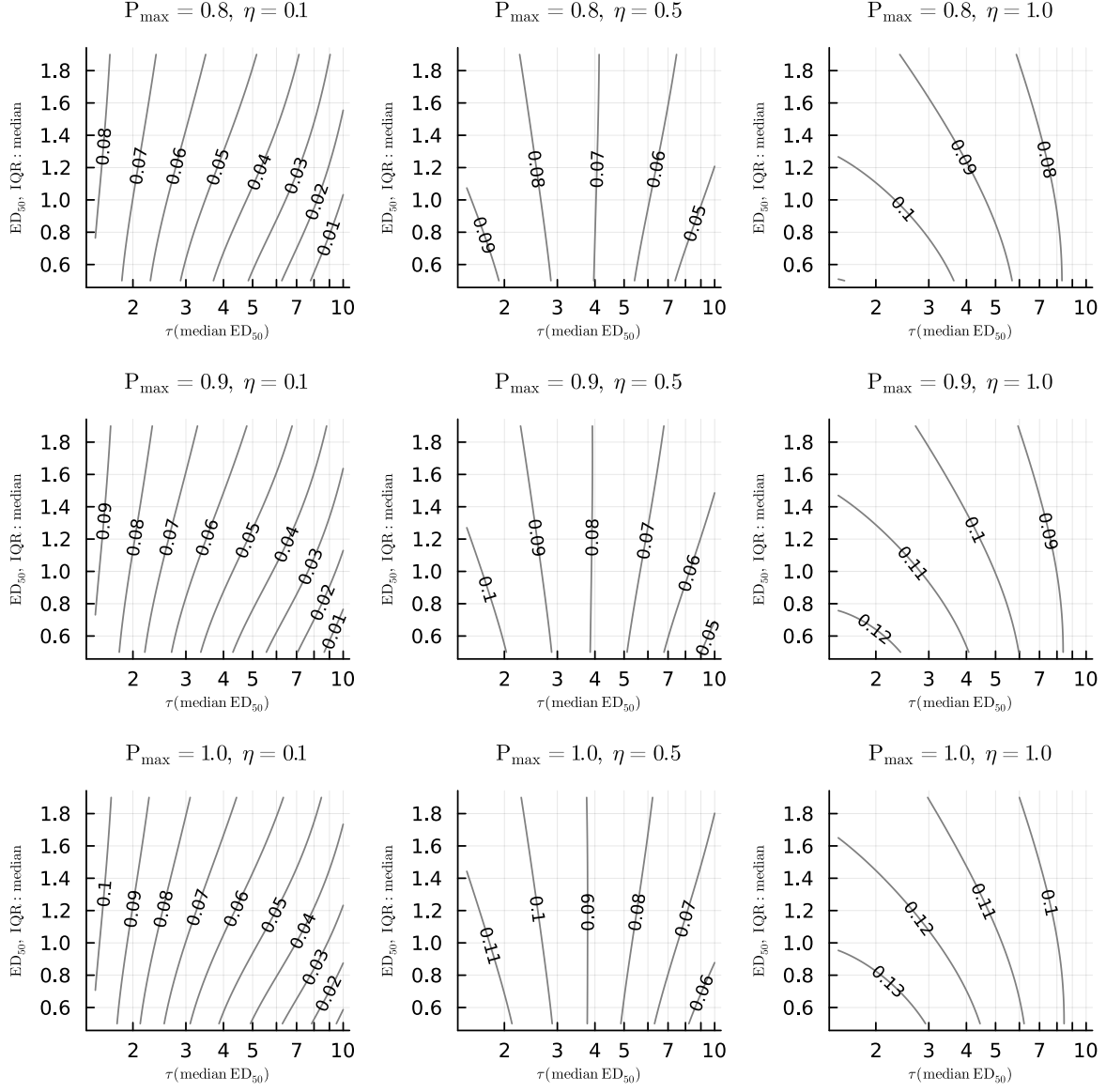


Figure S1: Per capita utility loss under optimal 1-size-fits-all dosing (Equation 12) as a function of drug tolerability and interindividual variability (IIV) in ED<sub>50</sub>, under the same combinations of ( $P_{\max}$ ,  $\eta$ ) depicted in Figure 3. The tolerability index  $\tau$  of Equation 8 is evaluated at median ED<sub>50</sub>; the ratio of interquartile range (IQR) to median is used to quantify IIV of ED<sub>50</sub>. An IQR:median ratio of 1 is assumed for the  $D^*$  parameter of Equation 2.

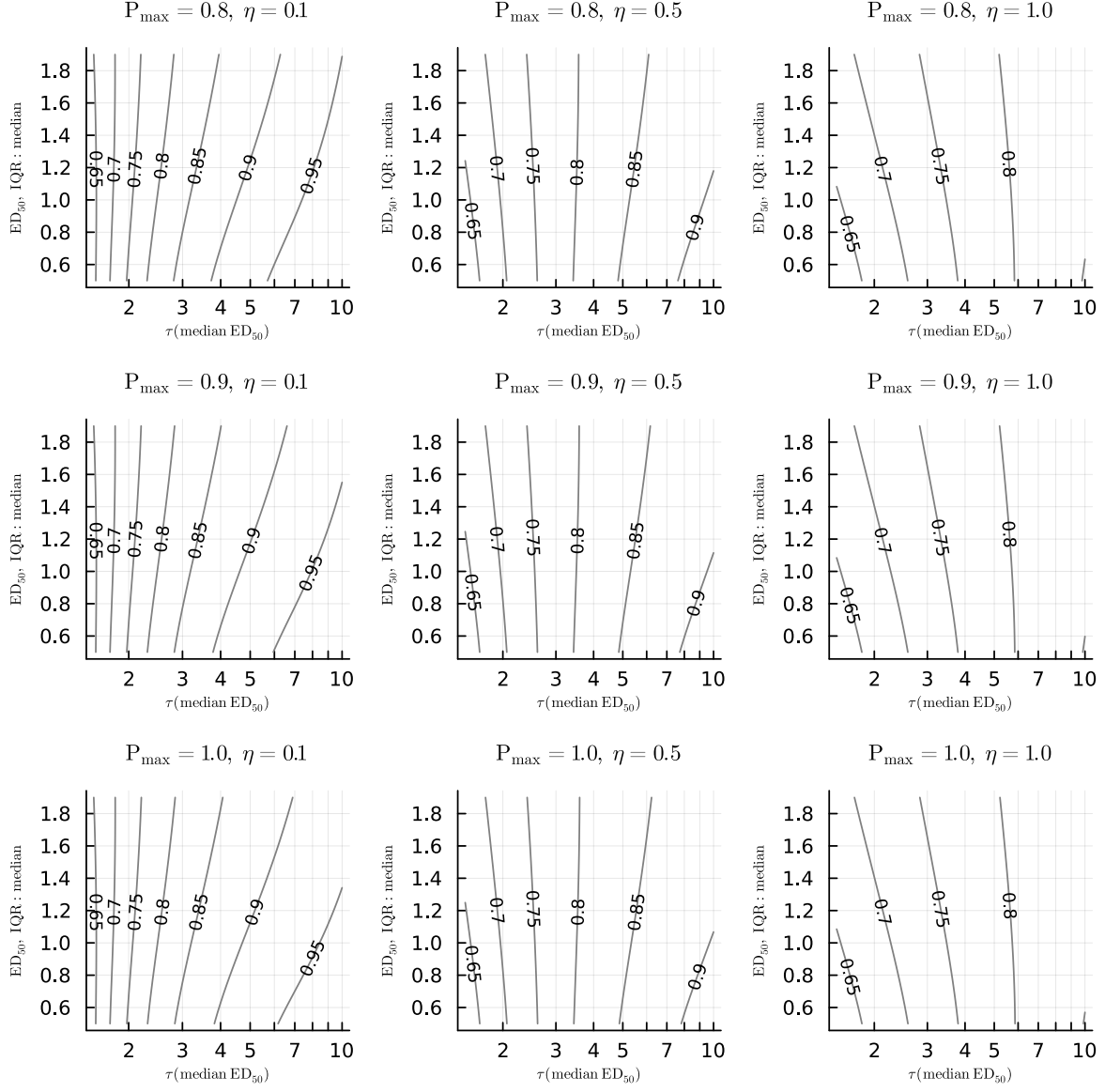


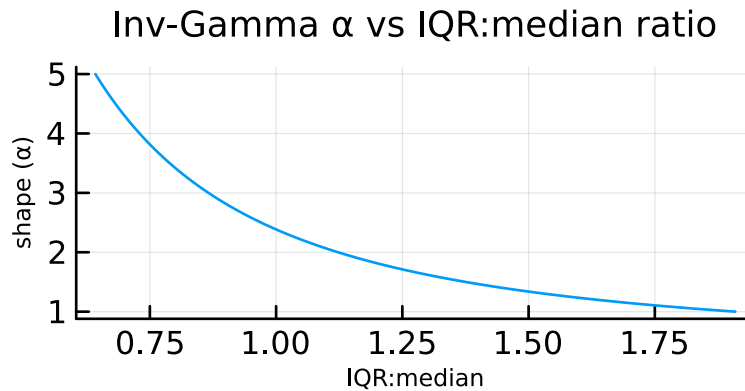
Figure S2: Efficiency of optimal 1-size-fits-all dosing relative to optimal individualized dosing, as a function of drug tolerability and interindividual variability (IIV) in  $\text{ED}_{50}$ , under the same combinations of  $(P_{\max}, \eta)$  depicted in Figure 3. The tolerability index  $\tau$  of Equation 8 is evaluated at median  $\text{ED}_{50}$ ; the ratio of interquartile range (IQR) to median is used to quantify IIV of  $\text{ED}_{50}$ . An IQR:median ratio of 1 is assumed for the  $D^*$  parameter of Equation 2.

### S3 A worked example

A reviewer rightly noted that a worked example would greatly help to build intuition about the magnitudes of the various quantities involved in the cascade of computation leading up to Figure 3. To this end, we will estimate the sample-size lower bound Equation 17 for a drug whose toxicities are characterized by  $\eta = 0.5$ , in a population where  $ED_{50}$  and  $D^*$  are both Inv-Gamma distributed with IIV given by IQR:median ratios of 1.2 and 0.85, respectively, and where the ratio of median  $D^*$  to median  $ED_{50}$  is 6.

To begin, there is a 1-1 relation between IQR:median and the shape parameter of the Inv-Gamma distribution:

```
let shape = 1.0:0.05:5
  iqr = [diff(quantile(InverseGamma(shp, 1), [0.25, 0.75]))][1]
  for shp in shape
    median = @. quantile(InverseGamma(shape, 1), 0.5)
    iiv = @. iqr / median
    plot(iiv, shape, size=(300,150), label=:none)
    title!("Inv-Gamma  $\alpha$  vs IQR:median ratio", titlefont=font(9))
    xlabel!("IQR:median", labelfontsize=6)
    ylabel!("shape ( $\alpha$ )", labelfontsize=6)
  end
```



Thus, the given IQR:median ratios fully determine  $\alpha$  and  $a$ :

```
α = α_IQR(1.2); a = α_IQR(0.85)
(α=α, a=a)
```

```
(α = 1.814329620184339, a = 3.0934036890094667)
```

By adopting a convention that all doses will be expressed in terms of  $ED_{50}$ , we can also immediately fix our Inv-Gamma scale parameters,  $\beta$  and  $b$ :

```
β = β1(α); b = β1(a)*6
(β=β, b=b)
```

```
(β = 1.4940654364670427, b = 16.60330363938081)
```

Let's verify that indeed  $\text{Inv-Gamma}(\alpha, \beta)$  and  $\text{Inv-Gamma}(a, b)$  have the desired properties:

```
median_ED50 = quantile(InverseGamma(α, β), 0.5)
```

```
1.0
```

```
IQR_ED50 = diff(quantile(InverseGamma(α, β), [0.25, 0.75]))[1]
```

```
1.1999999999999997
```

```
median_Dstar = quantile(InverseGamma(a, b), 0.5)
```

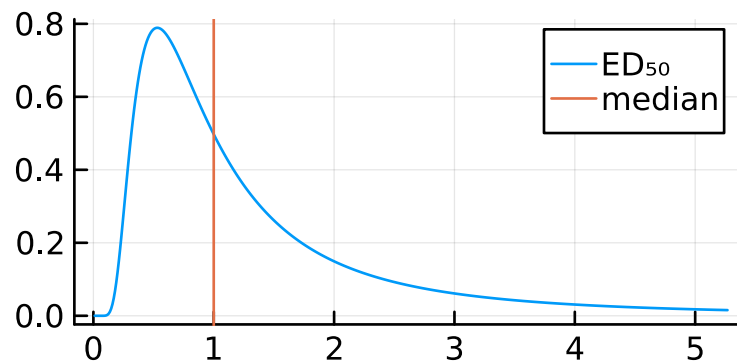
```
5.999999999999999
```

```
IQR_Dstar = diff(quantile(InverseGamma(a, b), [0.25, 0.75]))[1]
IQR_Dstar/median_Dstar
```

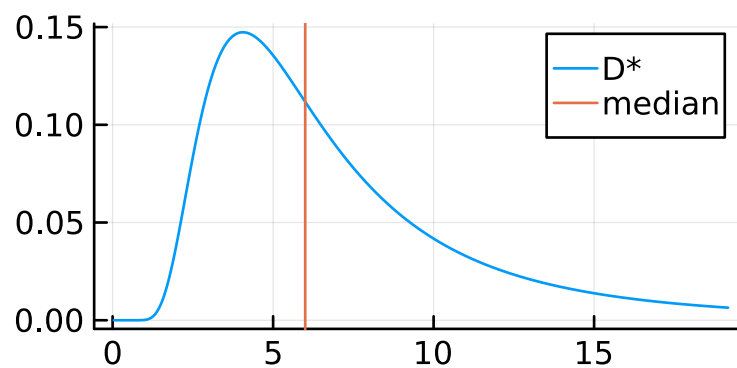
```
0.8500000000000003
```

We can now plot the distributions of  $ED_{50}$  and  $D^*$ :

```
let D = range(0.0, quantile(InverseGamma( $\alpha$ , $\beta$ ), 0.95), length=500)
dens = @. pdf(InverseGamma( $\alpha$ , $\beta$ ), D)
plot(D, dens, size=(300,150), label="ED50")
vline!([median_ED50], label="median")
end
```



```
let D = range(0.0, quantile(InverseGamma(a,b), 0.95), length=500)
dens = @. pdf(InverseGamma(a,b), D)
plot(D, dens, size=(300,150), label="D*")
vline!([median_Dstar], label="median")
end
```



If we suppose  $P_{\max} = 0.9$ , then we can now calculate  $\tau(\text{ED}_{50}) \equiv \tau(1)$  according to Equation 8:

```
P_max = 0.9
η = 0.5 # Note that η enters our calculations for the first time here
numer = 1 - (1+log(2)/β)^α
denom = gamma(a+1+η)/gamma(a) * (1/b)^(1+η)
τ = P_max * numer / denom
```

5.006499302927959

We can obtain the optimal 1-size-fits-all dose,  $\tilde{D}$ :

```
D_1 = Dtilde2(P_max=P_max, α=α, β=β, η=η, τ=τ)
```

1.5351194169051225

Since we have arbitrarily scaled our dose units to set median  $\text{ED}_{50} \equiv 1$ , we can interpret this to say the optimal 1-size-fits-all dose is about 1.5 times the median  $\text{ED}_{50}$  in the population.

If somehow (say, on the basis of preclinical and phase 1 studies) we have accurately predicted this optimal dose  $D_1$ , and wish to perform a dose-randomization trial of the kind described in Equation 15, then we will choose  $D_2$  via

```
D_2 = D_1 * 2^(1/(1+η))
```

2.4368501772920004

and evaluate Equation 16,

```
p_1 = P_max * (1 - (1 + D_1 * log(2)/β)^α)
p_2 = P_max * (1 - (1 + D_2 * log(2)/β)^α)
(p_1=p_1, p_2=p_2, Δp=p_2-p_1)
```

( $p_1 = 0.5607649904779122$ ,  $p_2 = 0.6718317844782518$ ,  $\Delta p = 0.11106679400033959$ )

to obtain  $n_{\min}$  via Equation 17:

$$q_1 = 1 - p_1; q_2 = 1 - p_2$$

$$8 \cdot (p_1 \cdot q_1 + p_2 \cdot q_2) / (p_2 - p_1)^2$$

302.71581271263483

Observe that this result corresponds to the point (5, 1.2) in the middle panel of Figure 3 lying nearly on the  $n_{\min} = 300$  contour.

Moreover, note that the additional 11% population-level efficacy at dose  $D_2$  incurs too high a cost in the form of expected toxicity:

```
G = gamma(a+1+η)/gamma(a)
ET1 = G*(D1/b)^(1+η)
ET2 = G*(D2/b)^(1+η)
(ET1=ET1, ET2=ET2, ΔET=ET2-ET1) # NB: ΔET = ET1 of course, since ET2 = 2ET1 by construction
```

(ET<sub>1</sub> = 0.1706753333862713, ET<sub>2</sub> = 0.34135066677254267, ΔET = 0.17067533338627136)

Finally, to unfold some insight into the heterogeneous individual perspectives underlying these population-average considerations, we plot the optimization problems for a grid of individuals situated at the  $3 \times 3 = 9$  combinations of the quartiles of  $D^*$  and  $ED_{50}$ :

```
# For given values of Pmax, ED50, D* and η, plot the utility and disutility curves,
# plus a line segment marking the individually optimal dose and ref lines for D1 & D2.
function utilindiv(; Pmax, ED50, Dstar, η)
    p = plot(size=(672,672))
    D = 0:0.1:6 # Note this is denominated in units of median(ED50) per our convention for β
    P = @. Pmax*(1 - 0.5^(D/ED50))
    T = @. (D/Dstar)^(1+η)
    plot!(D, P, label=:none)
    plot!(D, T, label=:none)
    τ = Pmax * (1 - (1+log(2)/β)^-α) * gamma(a)/gamma(a+1+η) * b^(1+η)
    D1 = Dtilde2(Pmax=Pmax, α=α, β=β, η=η, τ=τ)
```

```

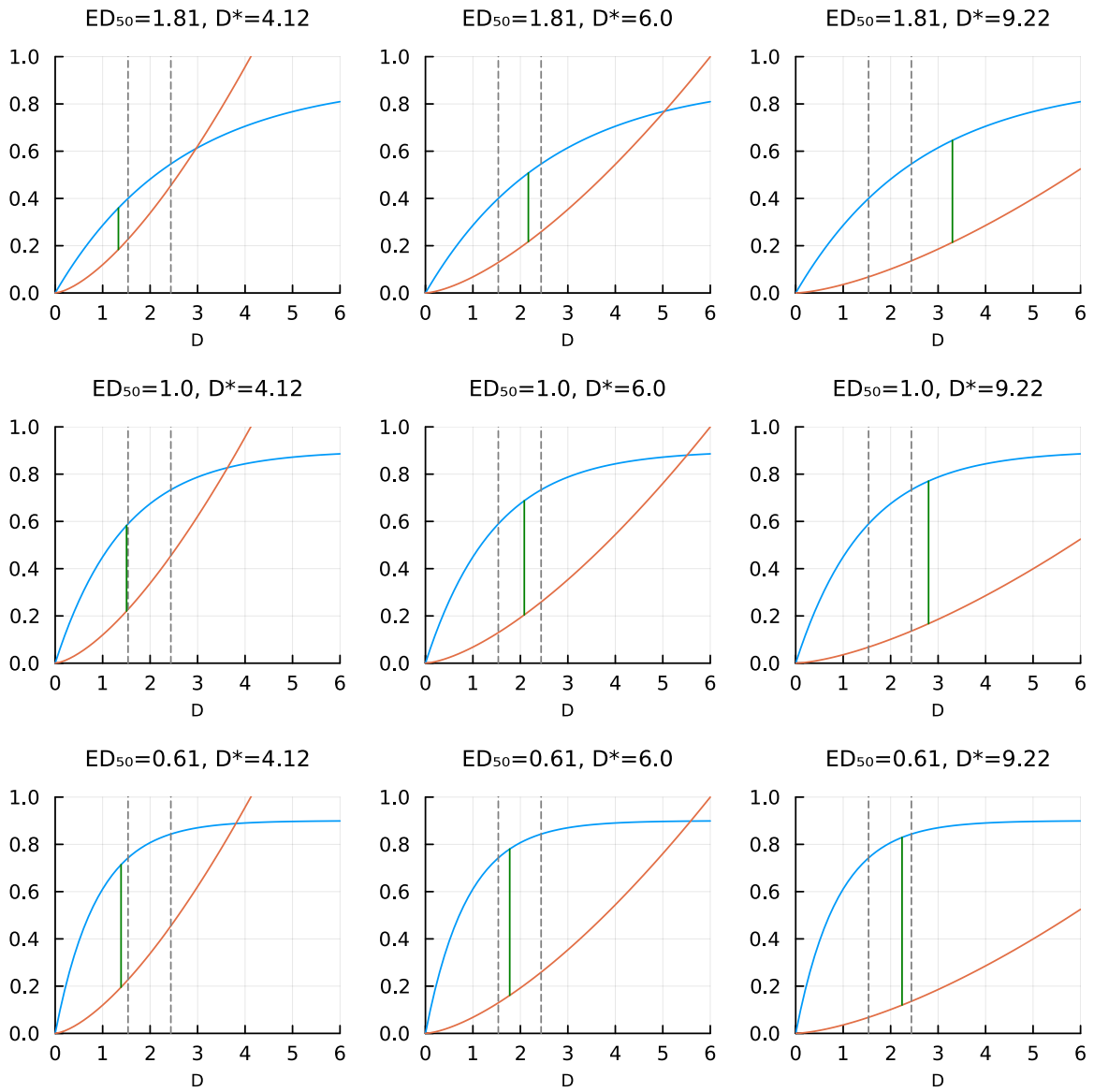
D2 = D1*2^(1/(1+η))
vline!([D1, D2], linestyle=:dash, linecolor=:gray, label=:none)
# Overplot a line segment at the individually optimal dose:
Di = Dhat(Pmax=Pmax, ED50=ED50, Dstar=Dstar, η=η)
PDi = Pmax*(1 - 0.5^(Di/ED50))
TDi = (Di/Dstar)^(1+η)
plot!([Di,Di], [TDi,PDi], linecolor=:green, label=:none)
title!("ED50=$ED50, D*=$Dstar", titlefont=font(9))
xlabel!("D", labelfontsize=7)

p
end

unfold(η) = plot(
    [utilindiv(Pmax=Pmax, ED50=j, Dstar=i, η=η)
    for i in round.(quantile(InverseGamma(a, b), [0.25, 0.5, 0.75]), digits=2),
    j in round.(quantile(InverseGamma(α, β), [0.75, 0.5, 0.25]), digits=2)
    ]..., layout=(3,3),
    xlims=(0,6), ylims=(0,1)
)

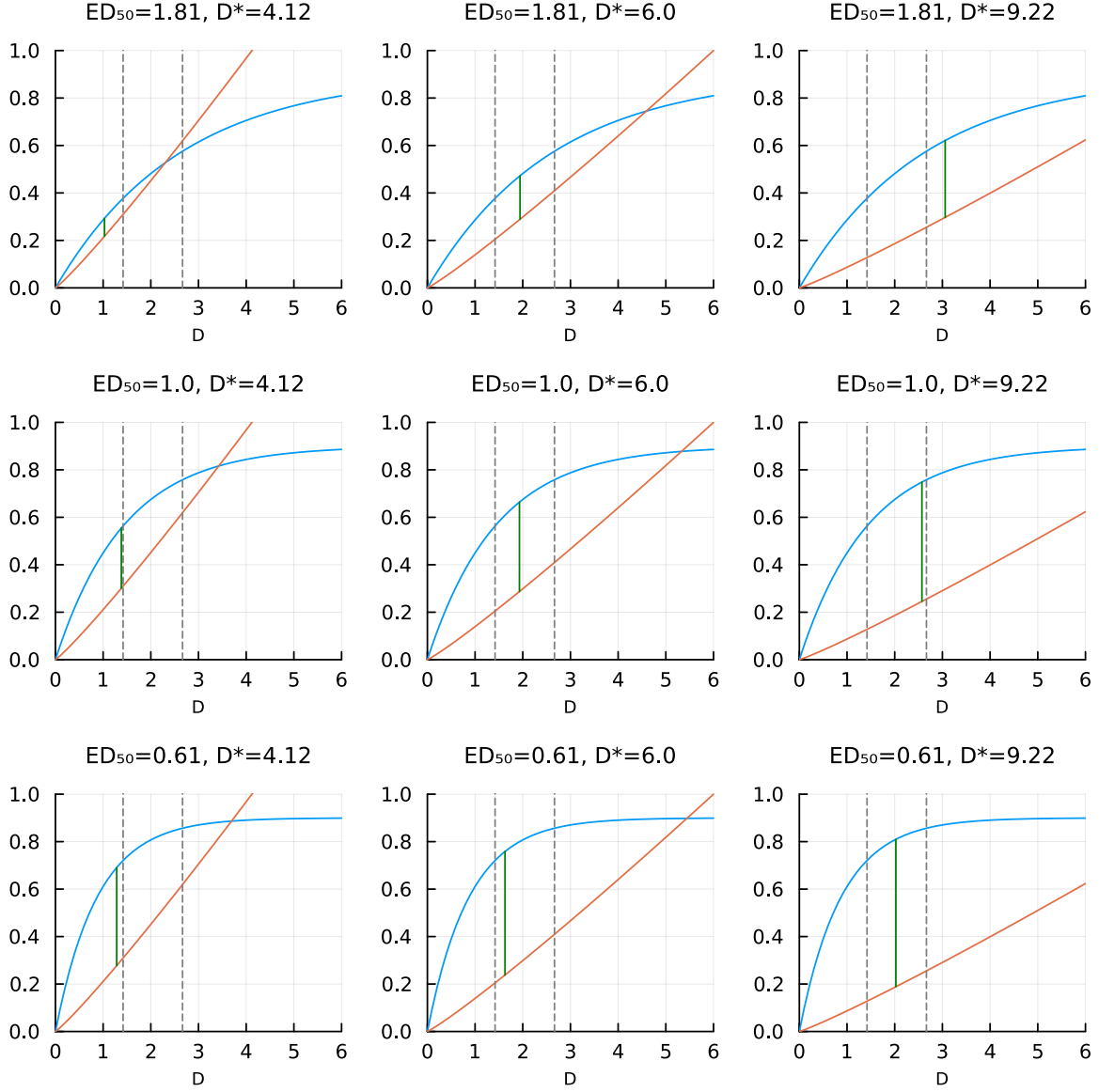
unfold(η=η)

```



For comparison, we offer this plot recomputed with  $\eta = 0.1$  and  $\eta = 1$ .

unfold( $\eta=0.1$ )



unfold( $\eta=1.0$ )

